

REMARKS

Status of the claims and formal matters

Claims 26-37 and 39-45 are pending in the instant application.

Claims 1-25, 38, and 46-50 had been previously cancelled. Claims 26, 29-31, 37, and 44 have been amended herein. New claim 51 has been added. The amendments of claims 26, 31, 37, and 44 are to correct obvious typographical errors. The amendments of claim 26 are supported on the bottom of page 4 and the top of page 5 of WO 04/024163. The amendments of claims 29 and 30 find support on the bottom of page 4 and the top of page 5 of WO 04/024163. The amendments of claim 31 are to label the three compounds previously depicted via chemical structures alone and are supported on pages 5 and 6 of WO 04/024163. Support for new claim 51 can be found in the fourth paragraph of page 7 of WO 04/024163. No new matter has been added as the result of these amendments.

It is submitted that the claims, herewith and as originally presented, are patentably distinct over the prior art cited by the Examiner, and that these claims are and were in full compliance with the requirements of 35 U.S.C. § 112. The amendment of the claims, as presented herein, is not made for purposes of patentability within the meaning of 35 U.S.C. §§ 101, 102, 103, or 112. Rather, this amendment is made simply for clarification and to round out the scope of protection to which Applicants are entitled. Furthermore, it is explicitly stated that the amendment presented herein should not give rise to any estoppel.

Claim rejections under 35 U.S.C. § 103

1. The Examiner maintains his rejection of claims 26-34, 36, 37, and 39-45 under 35 U.S.C. § 103(a) as being unpatentable over Leventer (US 6,649,607 B2) in view of Chenard, *et al.* (EP 0900568 A2). Specifically, the Examiner previously stated that "...because Leventer teaches that the administration of tofisopam treats convulsions and/or seizures including myoclonic jerks, it would be obvious to one of ordinary skill in the art to try, with a reasonable degree of success, to administer said drug to treat dyskinesia in view of Chenard's disclosure, which teaches dyskinesia as 'excessive abnormal movements that are involuntary' including chorea, tremor, dystonia, myoclonus, and tic." Applicant respectfully disagrees.

Leventer

Leventer describes compositions comprising and methods of treatment employing S-tofisopam to treat convulsions or seizures in a subject. The Examiner states that "...Leventer teaches that the administration of tofisopam treats convulsions and/or seizures including myoclonic jerks..." Applicant respectfully disagrees. In fact, in its "Background of the Invention" section, Leventer reports numerous studies indicating that tofisopam is not effective in the treatment of convulsions and/or seizures including myoclonic jerks: "The administration of tofisopam according to the tests described in Ito appeared to have no effect on decreasing the incidence of convulsions..." (US 6,649,607, column 2, lines 32-34); "Pellow et al reported that the administration of...tofisopam reduced the number of mice having convulsions...However, Pellow et al. also reported that all of the treated mice still experienced myoclonic jerks." (US 6,649,607, column 2, lines 38-43); and "Numerous other reports, some of which were published after 1986, state that tofisopam has no anti-convulsant properties..." (US 6,649,607, column 2, lines 55-57). Of note, all of these results are contextualized in terms of Leventer's purported invention – the use of the S enantiomer of tofisopam in corresponding treatment – as follows: "None of the studies tested the anti-convulsant activity of S-tofisopam substantially free of its (R) enantiomer." (US 6,649,607, column 2, lines 60-62). Nevertheless, because the majority of the studies described in Leventer's Background section indicated a lack of anti-convulsant activity on the part of tofisopam, the person of ordinary skill in the art would be taught away from employing tofisopam in such treatment. This teaching away is not reversed by the data provided in Leventer's examples. In fact, racemic tofisopam was used as a comparison point to illustrate the significant anti-convulsant effect of S-tofisopam. While racemic tofisopam did exhibit some intrinsic anti-convulsant activity against picrotoxin-induced seizures in male NSA mice, the S-tofisopam displayed significantly greater anti-convulsant activity than the racemate compound. Indeed, throughout the entire reference, Leventer consistently promotes the use of S-tofisopam substantially free of R-tofisopam.

The Examiner appears to imply that, because Leventer teaches that tofisopam administration effectively treats convulsions and/or seizures including myoclonic jerks (which Applicant strongly contests, as iterated above), and because Chenard includes a definition of dyskinesia as "excessive abnormal movements that are involuntary" including chorea, tremor, dystonia, myoclonus, and tic" (i.e., allegedly including myoclonic jerks), the ordinarily skilled

artisan would have a reasonable expectation of success in employing tofisopam to treat dyskinesia, including chorea, tremor, dystonia, myoclonus, and tic. Applicant respectfully disagrees.

The instant claim is directed to a method of treating dyskinesia, wherein the dyskinesia is manifest as chorea or dystonia. The Examiner focuses on myoclonic jerks. Myoclonus describes a medical sign and may develop in response to infection, head or spinal cord injury, stroke, brain tumor, kidney or liver failure, lipid storage disease, chemical or drug poisoning, as a side effect of certain drugs, or in response to other disorders. It can occur by itself, but it is most often one of a number of symptoms associated with a wide variety of disorders. Chorea and dystonia are distinct in neurological origin from myoclonus. They are also different phenomenologically, and they respond differently to pharmacological agents.

In particular, myoclonus (myoclonic jerks) describes paroxysmal, quick, lightning-like jerks (contractions) of a muscle or group of muscles akin to epilepsy or convulsions. Indeed, the rapid speed and brief duration of myoclonus are definitive for the disorder. In contrast, chorea is characterized by slow, sinuous writhing and dance-like movements that start in one part of the body and move abruptly, unpredictably, and, often, continuously to another part. In fact, the movements in chorea may merge imperceptibly into purposeful or semi-purposeful acts. Dystonic movements are associated with prolonged bursts of electrical activity in affected muscle(s), causing sustained abnormal postures and bodily contortions.

The underlying neuronal mechanisms of myoclonus are different from the mechanisms underlying the chorea and dystonia referred to in the instant patent application. The primary mechanisms by which chorea and dystonia are produced are different from the mechanisms underlying epileptic or convulsive activity. These fundamental differences can, for example, be borne out by the different responses observed to drug treatment. A pharmacological agent's efficacy for treating myoclonus has no predictive value in relation to its efficacy for treating chorea or dystonia. For example, myoclonus and other forms of convulsive, epileptic, or paroxysmal activity are treated with anti-convulsants. Anti-convulsants are, on the contrary, essentially not considered for the treatment of dyskinesias manifest as chorea or dystonia, since many studies actually indicate that they actually induce chorea or dystonia in patients. Likewise, drugs used in an effort to alleviate dyskinesia manifest as chorea or dystonia in patients are generally not used to treat myoclonus or convulsive activity.

Different types of movement disorders can develop, depending on the nature and location of damage to or malfunction of the central nervous system (brain and spinal cord), the nerves, and the muscles. For example, there can occur damage to the parts of the brain that control voluntary movement or the connections between the brain and spinal cord, resulting in weakness or paralysis of the muscles involved in voluntary movements and exaggerated reflexes. There can also occur damage to the basal ganglia, resulting in involuntary or decreased movements. There can also occur damage to the cerebellum, resulting in loss of coordination. And for each of the above-mentioned occurrences of damage, there are distinct movement disorders that may come about as a result of a specific subtype of damage. Thus, the person of ordinary skill in the art would not assume that several movement disorders could, with a reasonable expectation of success, be treated with a single agent. More specifically, the ordinarily skilled artisan would not reasonably expect that a therapeutic agent that reduces myoclonic jerks would be therapeutically effective against dyskinesia manifest as chorea or dystonia.

Thus, anti-convulsant efficacy of S-tofisopam does not reasonably indicate, either explicitly or implicitly, efficacy of S-tofisopam, let alone of tofisopam, in treating dyskinesia manifest as chorea or dystonia.

Chenard

Beyond its title “AMPA antagonists for the treatment of dyskinesias associated with dopamine agonist therapy” and similar sweeping statements throughout the reference itself, Chenard provides nothing substantive that shows or even implies that AMPA receptor antagonists can be used to treat dyskinesia resulting from the use of dopamine agonist therapy. Should the person of skill in the art be convinced by Chenard’s prophetic examples, he/she might believe that Chenard was in possession of the invention as claimed therein, i.e., “The use of a compound selected from groups (A), (B), (C), (D), (E), or (F) or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating dyskinesia associated with dopamine agonist therapy, wherein groups (A), (B), (C), (D), (E), and (F) are defined as follows...”.

Indeed, there is no enabling teaching in Chenard that compounds outside those in groups (A), (B), (C), (D), (E), and (F) are useful in the treatment of dyskinesia associated with dopamine agonist therapy. In this light, Applicant notes that, although the number of compounds speculated by Chenard for use in dyskinesia treatment is substantially large, the list of

compounds does not include the compounds described in U.S. Patent Application No. 10/527,271, for example, tofisopam. Furthermore, the compounds listed in Chenard have significant structural differences from the compounds of the present application.

In fact, compounds exemplary of those contemplated in the instant application for use in the treatment of dyskinesia manifest as chorea or dystonia, such as tofisopam, girisopam, and nerisopam, had, at the time of filing of the instant application, been shown by others to not have AMPA receptor antagonist activity. Tarnawa (copy provided herewith) states that tofisopam is not an AMPA receptor antagonist (page 58, left column, bottom third of third paragraph). Solyom (copy provided herewith) entitles tofisopam, girisopam, and nerisopam “Non AMPA antagonist type 2,3-benzodiazepines” (top of page 917). Thus, not only is tofisopam structurally distinct from the compounds of groups (A), (B), (C), (D), (E), or (F) in Chenard, but it also is distinct in terms of its activity – it does not exhibit AMPA receptor antagonist activity, whereas Chenard speculates exactly such activity for its compounds. Therefore, one of ordinary skill in the art would not consider tofisopam (as in Leventer) or a compound claimed in the present application as a compound in group (A), (B), (C), (D), (E), or (F) and would, thus, not be taught to treat dyskinesia associated with dopamine agonist therapy with Applicant’s compounds.

Furthermore, there is no enabling teaching in Chenard that a compound selected from groups (A), (B), (C), (D), (E), or (F) or a pharmaceutically acceptable salt thereof, let alone an AMPA receptor antagonist, can be used for treatment of a dyskinesia other than one associated with dopamine agonist therapy. Indeed, the prophetic example provided to assess the efficacy of the disclosed compounds relates to efficacy in the treatment of dyskinesia associated with dopamine agonist therapy, not any dyskinesia. Chenard does not provide any guidance with respect to the treatment of dyskinesias as described in [0002] of EP 0900568 A2: “...involuntary physical movements which may include chorea, tremor, ballism, dystonia, athetosis, myoclonus and tic.” Thus, the ordinarily skilled artisan is not left with a reasonable expectation that a compound selected from groups (A), (B), (C), (D), (E), or (F) or a pharmaceutically acceptable salt thereof, let alone any compound, let alone tofisopam, can be used effectively for the treatment of any involuntary physical movements, including chorea, tremor, ballism, dystonia, athetosis, myoclonus, or tic.

Thus, the combination of Leventer and Chenard does not provide an implicit motivation to or an explicit teaching of employ(ing) a compound as defined in the instantly pending claim 26 to treat dyskinesia manifest as chorea or dystonia.

It is further noted that, even assuming the Examiner's arguments and interpretation of the art are proper, Applicant still does not believe claim 26 to be obvious in light of Leventer and Chenard. The Examiner's argument relies on myoclonic jerks being recognized by one of skill in the art as being symptomatic of dyskinesia, i.e., if a compound treats myoclonic jerks, it should treat dyskinesia (manifest as chorea or dystonia) "regardless of whether the dyskinesia results from the actual symptoms of a disease...or whether the dyskinesia is a side effect observed upon administration of an agent used to treat a particular disease..." However, because myoclonic jerks constitute a ubiquitous sign of numerous disorders, as iterated above, an ordinarily skilled artisan would understand, in fact, expect, that the number of compounds that could affect myoclonic jerks associated with so many disease states or disorders would be extensive to the point of requiring undue experimentation to test each and every one of them. Indeed, beyond compounds ostensibly targeting the myoclonic jerks themselves, compounds useful in the treatment of stroke, heart attack, kidney failure, etc., could all, under the Examiner's rationale be administered as treatment for dyskinesia. This would present the ordinarily skilled artisan with an unreasonable standard given to a large number of unrelated compounds as possible therapeutics. Indeed, this is borne out in Chenard, which speculates a chemically unrelated group of compounds (in comparison with Applicant's compounds) for use in the treatment of dyskinesia. Accordingly, one of skill in the art would be utterly unmotivated to target myoclonic jerks as a trigger point for testing compounds to treat dyskinesia as broadly defined according to Chenard, let alone manifest as chorea or dystonia.

If an independent claim is non-obvious under 35 U.S.C. § 103, then any claim depending therefrom is non-obvious. *In re Fine*, 837 F.2d 1071, 5 U.S.P.Q. 2d 1596 (Fed. Cir. 1988). Having established the non-obviousness of claim 26, claims 27-34, 37, 37, and 39-45 are, by extension, also non-obvious. Accordingly, Applicant respectfully requests that the instant rejection under 35 U.S.C. § 103 be withdrawn.

2. The Examiner maintains his rejection of claim 35 under 35 U.S.C. § 103(a) as being unpatentable over Leventer (US 6,649,607 B2) in view of Chenard, *et al.* (EP 0900568 A2) and in further view of the "PD website". Specifically, the Examiner states that "It would

have been obvious to one of ordinary skill in the art at the time of the invention that employing the treatment of dyskinesia associated with parkinsonism as discussed above, that one would have necessarily been treating idiopathic Parkinson's disease."

PD website

The PD website fails to cure the defects of Leventer and Chenard. The Examiner relies on the PD website for its statement that the most common type of parkinsonism is idiopathic Parkinson's disease, whose cause is unknown. However, the website does not provide data showing that tofisopam can be used as an anti-convulsant. Nor does the website provide any reasoning as to why the ordinarily skilled artisan might expect a therapeutic agent effective in the treatment of myoclonus to likewise demonstrate efficacy in the treatment of dyskinesia manifest as dystonia or chorea.

Thus, the combination of Leventer and Chenard and the PD website does not provide an implicit motivation to, or an explicit teaching of, employ(ing) a compound as defined in the instantly pending claim 35 to treat dyskinesia manifest as chorea or dystonia. Accordingly, Applicant respectfully requests that the instant rejection under 35 U.S.C. § 103 be withdrawn.

CONCLUSION

This constitutes a request for any needed extension of time and an authorization to charge all fees therefor to deposit account No. 19-5117, if not otherwise specifically requested. The undersigned hereby authorizes the charge of any fees created by the filing of this document or any deficiency of fees submitted herewith to deposit account No. 19-5117.

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Respectfully submitted,
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